THEOPHYLLIN AS A DIURETIC.*

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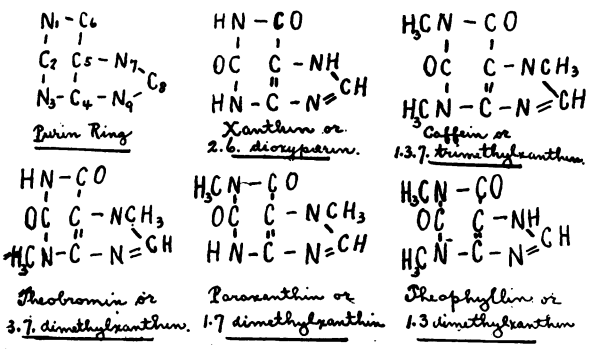
Theophyllin is beyond doubt the most remarkable diuretic that we possess today. Though the drug occurs naturally in tea in small amounts, its wide medicinal use has only been made possible by its synthetic preparation. This synthetic product is placed on the market under the trade name of theocin.

The first clinical report on the diuretic use of theophyllin was published by Minkowski in November, 1902 (1). This was followed rapidly by favorable reports from numerous German clinicians (2, 3, 4, 5, 6, 7, 8, 9), as well as by many reports from Italian and a few from French observers. Curiously enough, very few articles have appeared on this subject in the English or American literature, though it is probable that the drug has been considerably used in these countries. In the present paper I propose to review some of the literature dealing with theophyllin and to present some personal observations on its use, with the hope of interesting those who have not used it, and of promoting discussion among those who have.

Theophyllin belongs to the caffein-theobromin group of diuretics. The chemical relations between the members of this group may, perhaps, be best appreciated by a little study of their rather complex formulæ (taken from 3). Starting from E. Fischer's purin ring with its nine numbered positions, we have first xanthin or 2.6. dioxypurin; i. e., the second and sixth positions of the purin ring are occupied by oxygen. Caffein



is 1.3.7. trimethylxanthin, the methyl groups taking the first, third and seventh positions on the purin ring. It is evident that by removing each of these methyl groups in turn we shall have three different dimethyl xanthins. Thus the 3.7. dimethyl xanthin is theobromin, which is extensively used as a diuretic, more especially as its sodium salicylate salt (diuretin) and as its sodium acetate salt (agurin). The 1.7. dimethyl xanthin or paraxanthin has been shown to possess marked diuretic properties upon animals (10) though apparently it is less effective on man (11). The last, or 1.3. dimethyl xanthin, is theophyllin, in which we are particularly interested today. It is sold under the trade name of theocin and is used either as the pure drug or as its sodium acetate salt.

The diuretic action of theophyllin can be shown even on the normal man (12). Therapeutically, it is used to remove fluid from the body, such as edemas, exudates, and transudates. The most favorable cases for its use are undoubtedly the cardiac dropsies. I have used theophyllin in the treatment of three patients with edema due to mitral diseases, and in all the results were most satisfactory.

As an example of the exceedingly good effects obtained in some cases, I may recite the history of a patient whom I have seen recently in consultation with Dr. Wm. Flint of Santa Barbara. A woman about 45 years old had been troubled for some years with shortness of breath and had been told some time ago that she had heart disease but that her urine was normal. For several weeks past she has been gradually getting worse and at the present time she is unable to sleep on account of dyspnœa. Her legs have become extremely swollen, her face is puffy. There is considerable fluid in her left chest and in her abdominal cavity. The heart shows the typical signs of mitral insufficiency. Its action is extremely irregular, about 120 to the minute. Venous tracings show a positive venous pulse, probably due to a tricuspid insufficiency, though we could not exclude the possibility of an atrio-ventricular inception of the cardiac rhythm (13). Liver enlarged and tender but not distinctly pulsating. Urine 10 to 20 oz. a day and contains 1½ gm. of albumin to the liter and no casts. The diagnosis was made of a primary valvular mitral insufficiency with secondary passive congestion of the kidney. Patient was given a three days' course of the well-known pills of digitalis, squills, and calomel. This increased her urine to about 32 oz. per day. On the fourth day she was given 5 grains of theocin sodium acetate after breakfast and the dose was repeated after lunch. On this day she passed 85 oz. of urine. A second course of digitalis held her urine at about 40 oz. per day. The second day of theophyllin caused her urine to rise to 155 oz., or nearly five quarts, in twenty-four hours. By this time the edema, the hydrothorax, and the hydroperitoneum had completely disappeared. The pulse was considerably slower and more regular, and the patient's serious symptoms were gone. Subsequent courses of digitalis followed by the theophyllin increased the urine moderately, but nothing like what had been done on these two occasions.

Another patient who had mitral insufficiency and stenosis with badly broken compensation and with general edema, was given the infusion of digitalis for a time, with marked benefit. Gradually, however, the edema and hydrothorax reappeared. He was then given fifteen grains of theophyllin during the course of a day, with the result that he passed five quarts of urine in 24 hours. During the night following he was very nervous, restless, and at times delirious.

On three occasions I have used theophyllin on patients with myocardial disease and edema. In all the drug produced a marked effect. The most pro-

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nounced results were obtained in a patient seen at the medical clinic of the Cooper Medical College on August 8th, 1906. He was 64 years old, alcoholic, suffering from dyspnœa and from the cough and sputum of chronic passive congestion of the lungs. He was slightly cyanosed and slightly jaundiced; marked edema of the legs. His heart was very much enlarged downwards and to the left and on auscultation a systolic murmur was heard at the apex and the second pulmonic sound was markedly accentuated. Pulse extremely irregular, many beats of the heart not reaching the wrist. Jugular veins swollen and showing on tracings a positive venous pulse. Liver at the level of the umbilicus. Urine much diminished but shows neither albumin nor casts. Four days' use of the infusion of digitalis raised the quantity of urine to an average of two quarts a day. On the fifth day he took 15 grains of theophyllin and within 24 hours he passed seven quarts of urine. He was unable to sleep during the night because he passed urine so freqeuntly. In the morning he appeared at the clinic, a shadow of his former self. The edema had completely disappeared; and although he was kept under observation for several months it did not return in any amount. His pulse did not become regular. The systolic murmur at the apex subsequently disappeared and the patient's main complaint then became pain in the region of the heart. I believe that he was suffering from myocardial disease dependent upon coronary sclerosis.

For over two years I have had under my care a patient with cardiac insufficiency, apparently due to pericardial adhesions. He has had pleuritic exudates on both sides for which he has been tapped between fifteen and twenty times. The large amount of albumin in these exudates and the almost exclusive presence of lymphocytes makes it probable that these exudates are of a chronic inflammatory character. More recently this patient has been tapped for ascites, possibly due to his well marked cardiac cirrhosis. During the two years that this patient has been under my care, he has taken theophyllin on the average of once a week. Until the ascites became marked its use was always followed by an increased elimination of urine, the amount frequently rising from 20 to 60 oz. for the day. He objects to the drug because it often causes nausea and makes him feel very nervous.

I have come to regard theophyllin as an extremely active and almost certain diuretic in cardiac dropsy. It has also been recommended for nephritic edemas though here its action is generally regarded as less certain (8, 14). My own experience in employing it for these dropsies has not been encouraging. I have used it or seen it used in at least seven patients, and in none was sufficient diuresis produced to warrant its continued use. Although I have never had an opportunity to use theophyllin for the edema of acute nephritis, nevertheless a few remarkable successes in the literature (4, 9) would justify one in trying it in such conditions.

Edemas due to anemia, malignant disease, etc., are in some instances very favorably influenced by the administration of theophyllin. Thus in a patient under my care recently with a malignant tumor in the region of the left kidney, with edema of the legs and face, fluid in the peritoneal cavity and a hemorrhagic exudate in the left pleura, the amount of urine averaged 22 ounces per day before the administration of theophyllin, whereas during the daily administration of 15 grains of the sodium acetate salt the quantities passed per day were 71, 88, 77 and 50 ounces. During these four days the edema and the peritoneal exudate disappeared, but the hemorrhagic pleuritic exudate did not seem to be markedly influenced.

Pleural and peritoneal effusions due to local causes are not particularly favorable for the use of theophyllin. A few authors (6) have obtained good results in cases of tuberculous pleurisies, the exudate rapidly disappearing; but in general the diuresis does not suffice to remove the exudate. I have used it in two patients with tuberculous pleurisy, in one of whom there was an associated pericardial exudate. Although the urine was moderately increased in each, tapping had to be resorted to finally. When we desire to treat such a patient by dry dieting, restriction of chlorides, saline purgatives, etc., with the object of reducing the water in the body, the administration of theophyllin would seem to be rational, for in this way the elimination through the kidneys may be kept at a higher level. The ascites of hepatic cirrhosis is rarely influenced by theophyllin. I have seen one patient, however, where it seemed quite certain that the theophyllin assisted to dispose of an ascites of this character. After its use no further tappings of the abdomen were necessary.

How does theophyllin produce diuresis? Like other members of the caffein group of diuretics its action can not be accounted for by any improvement in the general circulation. It does not affect the blood pressure to any marked degree either in animals or in man (5, 8). I have determined the systolic and dastolic blood pressures in a patient both before and during a marked theophyllin diuresis without being able to detect any change. It seems certain that these diuretics act in some manner on the kidney itself. It has been shown experimentally that during their action the kidneys increase very decidedly in volume and that more blood passes through them (15).

Caffein actively dilates the renal vessels by its direct action on their walls (15). The increased rate of flow through the kidney causes an increased excretion of urine. Whether this is the sole cause of the theophyllin diuresis or whether there is in addition a direct stimulation of the secreting cells has not yet been definitely decided. There is evidence that the resorbtion of edema and exudates under the influence of theophyllin is dependent not only upon its renal action, but upon an active resorbtion of fluid from the periphery. Thus if theophyllin be injected into rabbits with tied ureters a dilution of the blood takes place, its organic constituents becoming diminished and its salts increased (16).

This has been held to indicate an active resorption of fluid from the tissues through the walls of the capillaries.

Owing to the fact that theophyllin does not affect the circulation to any great extent, it is frequently combined with digitalis, especially when the edema is caused by a cardiac insufficiency. The digitalis is best given for three or four days in order to improve the general circulation, and immediately afterward the theophyllin is given. Sometimes the latter alone is almost without action, whereas if preceded by digitalis marked diuresis is obtained (8).

The fact that theophyllin acts locally on the kidneys and that it is believed by many to stimulate the renal cells to increased activity has given rise to the suspicion that it may do injury by over-irritation of the kidneys. The few reported cases that admit of such a possible interpretation (2) are not at all convincing, however; and, on the other hand, nearly every writer on this subject has expressed his conviction that theophyllin can be used with impunity in nephritis, and that while it may not do good, at least it never does harm. I have already related the history of a patient whose urine showed one-half gram per liter of albumin as a consequence of chronic passive congestion. Following the use of digitalis and theophyllin the albumin almost disappeared. I am able to cite another similar case which occurred in the service of Dr. J. O. Hirschfelder. A man with cardiac insufficiency due to muscular disease showed ½ gram of albumin to the liter and hyaline casts before treatment. Under the use of theophyllin he passed large quantities of urine, his edema vanished and the albumin and casts disappeared from his urine. It seems to me that such cases as these, together with its successful use in acute nephritis make it improbable that theophyllin damages the kidneys. When we consider that this drug accelerates the renal circulation, it seems quite as probable that it may do good rather than harm.

The diuretic action of the various members of the caffein group have been compared on animals by Ach (10). The following figures represent the amount of urine passed as compared with the normal:—caffein, 2.7; diuretin, 3.8; paraxanthin, 7.8; theophyllin, 6.3; xanthin, 1.7, etc. Clinical experience has abundantly shown that in man also theophyllin is a more active diuretic than is caffein or the theobromin compounds, diuretin and agurin. Various authors (3,12) have alternated these different diuretics on the same patient and almost invariably it has been found that theophyllin produced a greater diuresis than any of the others. Its tion begins more promptly, within a few hours, and its effects do not last so long. However, the notorious uncertainty of diuretics appears at times, and theophyllin is in some cases surpassed by other drugs of this group. Paraxanthin, which promised so much from Ach's observations on animals, has recently been placed on the market as a dimethylamino compound under the trade name of paraxin, but its efficacy so far as man is concerned does not seem to equal that of theophyllin (11).

Objection has been made to theophyllin on the ground that it soon loses its efficacy. This seemed to be the case in several of my patients. The marked diuresis obtained during the early use of the drug was followed by less and less effect, until finally it had almost no action whatever. Schmiederberg (17), who believes that it does not lose its effect, attributes the lessened diuresis to the lessened quantity of water in the body; but it seems to me that this is not the only explanation. Loewi has shown that a similar tolerance for caffein may develop in animals and that this is associated with a lessening of the dilatation of the renal vessels after repeated doses of the drug (15). Since theophyllin tends in time to lose its effect, it is unwise to continue its administration too long. After giving it for one to three days a rest of several days should follow.

Unfortunately theophyllin sometimes produces discomforting and even alarming symptoms. Of these the most common are gastric distress, nausea and vomiting. Diarrhœa is less frequent. In order to avoid these gastric symptoms it is best to give the less irritating sodium acetate salt and to dissolve in a large quantity of water. More serious than the gastro-intestinal are the nervous symptoms which sometimes follow the use of theophyllin. An increased nervousness, such as is seen after drinking too much coffee, is not uncommon, and this may go on to delirium, as happened in one of my patients, and in some cases it even goes on to convulsions. Schlesinger (14) was able to collect fifteen cases from the literature and from his personal experience where convulsions followed the use of theophyllin; and although in some of these the etiological relation was not certain (18), there can be little doubt that convulsions sometimes follow its use. For this reason care should be exercised in giving theophyllin to uremic patients, as well as in giving it to those who respond to its use with excessive nervousness. Nervous symptoms of a mild character may be controlled by the use of such hypnotics as chloral or pareldehyde. Some of the more recent writers on this subject, warned by the occurrence of convulsions, have adopted much smaller doses than are usually prescribed. Instead of five grains three times a day they give only one-third grain (9). The immediate diuresis resulting from this small dose is not so pronounced, but the drug continues to be efficient over a longer period of time, so that in the end the result is much the same.

In conclusion, I may say that we have in theophyllin a drug which possesses remarkable diuretic properties, and one which should be tried early in the often fruitless search for an effective diuretic. The fact that it acts within forty-eight hours at the most allows us to decide early whether we shall continue its use or not. In this respect it is superior to diuretin; for a number of days are necessary to decide the value of that drug. I have come to regard theophyllin as an almost certain diuretic for edemas of cardiac origin, and in such patients I always precede its use by three or four days of digitalis. For edemas of other origin, theophyllin, though often a failure, is always deserving of trial. Should it fail to act, other drugs of this same group, such as

diuretin, agurin and paraxanthin, may be tried; for unfortunately we can not reason that because one has failed another will do the same. Perhaps no part of therapeutics is more full of surprises than is this of the practical use of diuretics. In theophyllin, however, we possess one of the most reliable drugs of this field.

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Discussion.

Dr. J. B. Frankenheimer, San Francisco: I have tried this drug in several cases at the suggestion of Dr. Hewlett, and have found it very successful. We have had astonishing results with it.

Dr. R. L. Porter, San Francisco: I have not had any personal experience with it, but have seen it used by Dr. Shiels, of San Francisco. He says in giving theophyllin it is always necessary to give a mercurial compound. There is a question of diuretics in acute nephritis. The use of caffein has been tried and the use of diuretin, and both abandoned because by the use of a hot pack properly given and endoclysis, such good results have followed.

Dr. E. W. Twitchell, Sacramento: It seems to me that we have heard too little about the reverse side of this question. I have tried this drug on a number of my patients. There is no question about the diuretic effects, but the extreme effects were such that I abandoned its use. The patients almost invariably complain of severe nausea and vomiting. I have tried to overcome it, and have tested my patients by administering it in one form or another, but it almost always produced persistent nausea and it became necessary to abandon it.

Dr. L. J. Belknap, San Jose: I have never had any particular experience with this particular drug, but have had to do with a good many cases of cardiac dropsy, and as a rule I have met with good success by the use of the packs, and especially the electric light bath with friction salt to keep the skin active and if possible to do something in a curative way, rather than something only to remove the symptom. I have cleared up the trouble in this way, and it has remained so. I find it to advantage to keep these patients in bed, on milk diet, especially buttermilk, and by use of such treatments and keeping up the tonic treatments, I have had good success. I think we are liable to give treatments of a depressive nature of too great severity and too long continued.

Dr. W. W. Kerr, San Francisco: I think it is hardly fair to mix up the subject of this paper with that of dropsy in general. I do not think Dr. Hewlett said anything about rdopsy in general. He spoke merely of one drug and of those drugs of the group. Certain cases of dropsy are suitable to the bath treatments and certain others to other different treatments. The only trouble I have had with this drug has been the intense nervous excitement produced in some patients. Some patients can take but comparatively small doses. The same thing is noticed in caffein. I have seen one grain of caffein set a patient up for the whole day. I remember giving three grains to another patient with but slight excitement. There is one point about which I wish we knew something more, and that is the relation between the drug as it is given in the hypodermic form (there are a good many experiments being done on animals), and when given by the stomach and the different sorts used. For years I have noticed that the caffein would produce a good deal of trouble in the stomach. On the other hand, hypodermically, that was not produced. Whether it is the proportion given by the stomach which undergoes certain charges when given in the form of citrate, or whether it is the alkaloid that is affected, I do not know. In some cases the citrate of caffein increased the albuminuria, while hypodermically it did not have that effect.

Dr. W. E. Bates, Davisville: I have used this extensively and have now a patient with mitral insufficiency who is taking six doses a day of the theosin acetate. I would like to ask what mixture Dr. Hewlett uses in the liquid form.

Dr. Hewlett, closing discussion: The main remarks that have been made seem to be about the disagreeable features. A drug able to produce such marked effects is worthy of trial, and it is worth our while to get rid of the accessory symptoms. I think I covered the points in my paper more or less in regard to the gastric disturbances. Some patients can not take it. The gastric distress also is less if given in a solution rather than in powder form. It dissolves very readily and can be given with some form of peppermint in water. If a patient becomes delirious, then more must not be given of the drug. The drug can be given in much smaller doses. The most serious objection is that some patients have convulsions and some authors think the patients die in these convulsions, but I went over the history of such a case, and do not think the drug was the cause of the convulsions. If you wish to be cautious you should administer smaller doses, 1 to 3 grains t. i. d., or combine it with chloral, a drug which controls the central nervous system.

GROCCO'S SIGN.*

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Notwithstanding the efforts of the best observers of clinical phenomena in the past, it has fallen to the lot of Grocco of Florence to note and describe a new and very valuable physical sign of pleural effusion. It is rather astonishing that such an obvious sign should have been overlooked so long, and, aside from its worth, it shows that there is still room for discovery by the pure clinician, and fur-

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